CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PYRIMETHANIL

Chemical Code # 5864, **Tolerance #** 52950
SB 950 # NA

4/18/05

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, rat:	No data gap, possible adverse effect indicated.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Acceptable studies are not required at this time.

Toxicology one-liners are attached.

All record numbers through #205801 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T050418
Revised by T. Moore, 4/18/05

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 0145, -0146, -0147; 205781, 205782, 205783**; "Technical SN 100309: 104 Week Rat Combined Chronic Toxicity and Oncogenicity Study"; (S.J. Rees; Schering Agrochemicals Limited, Chesterford Park, Saffron, Walden, Essex CB10 1XL, Great Britain; Report Nos. A81806, A54965, A81808; 4/22/93); Fifty Sprague-Dawley rats/sex/group received 0, 32, 400 or 5000 ppm of Technical Grade SN 100 309 (code/batch no. CR 19325/01/900304, purity: 97.2% (3/12/90), 96.8 (8/25/92)) in the diet for up to 24 months ((M) 0, 1.3, 17, 221 mg/kg/day, (F) 0, 1.8, 22, 291 mg/kg/day). Additional groups of 20 animals/sex/group received the test material in the diet for 12 months. The treatment did not affect the survival of the treated animals. The mean body weights and food consumption of both sexes in the 5000 ppm group were less than those of the controls throughout the study ($p<0.05$). There were no treatment-related effects noted in the ophthalmology or urinalysis examinations. In the hematology evaluation, the mean hemoglobin and/or hematocrit values of both sexes in the 5000 ppm group were less than those of the controls at various times throughout the study ($p<0.05$). The mean white blood cell count of the 5000 ppm males was lower than that of the controls at 18 and 24 months of the study ($p<0.05$) with an accompanying decrease in neutrophils ($p<0.05$). In the clinical chemistry evaluation, the mean serum albumin levels were elevated for both sexes in the 5000 ppm group at various times throughout the study ($p<0.05$, 0.01 or 0.001). The mean serum phosphate levels of the males in all of the treatment groups were less than those of the controls throughout the study period ($p<0.05$, 0.01 or 0.001). In contrast, the mean potassium levels for the males in these groups were greater than those of the control at various times during the study ($p<0.05$, 0.01 or 0.001). The mean serum urea levels were elevated for the males in all of the treatment groups at various times during the study ($p<0.05$, 0.01 or 0.001). The mean serum cholesterol and total bilirubin levels of the 5000 ppm females were greater than the control values throughout the study ($p<0.05$, 0.01 or 0.001). The mean relative liver weights of both sexes in the 5000 ppm group were greater than those of the controls at both 12 and 24 months ($p<0.01$). The mean absolute liver weights for the 400 and 5000 ppm males were greater than those of the controls at 24 months ($p<0.05$ or 0.01). The mean relative kidney weights of the 5000 ppm males at 12 months ($p<0.01$) and of the 5000 ppm females at 24 months ($p<0.05$) were greater than those of the controls. In the histopathology examination, the liver and the thyroid gland were the target tissues. Centrilobular hypertrophy was evident primarily in the livers of the 5000 ppm males ((M) 0: 0/70 vs. 5000: 52/70, (F) 0: 0/70 vs. 5000: 7/70). An increased incidence of eosinophilic foci was noted in the livers of both sexes in the 5000 ppm group ((M) 0: 2/70 vs. 5000: 20/70, (F) 0: 7/70 vs. 5000: 14/70). In the thyroid, deposition of brown pigment was evident for both sexes in the 5000 ppm group ((M) 0: 1/70 vs. 5000: 56/70, (F) 0: 1/70 vs. 5000: 66/70). There was an increased incidence and severity of hypertrophy of the follicular epithelium for both sexes in the 5000 ppm group ((M) 0: 34/70 vs. 5000: 54/70, (F) 0: 21/70 vs. 5000: 51/70). In addition, the incidence of colloid depletion was greater and more severe in both sexes of the 5000 ppm group ((M) 0: 34/70 vs. 5000: 54/70, (F) 0: 21/70 vs. 5000: 51/70). The incidence of follicular cell adenomas was greater for both sexes in the 5000 ppm group ((M) 0: 3/70 vs. 5000: 10/70, (F) 0: 0/70 vs. 5000: 7/70). In addition, one of the males in the 5000 ppm group also suffered from a follicular cell adenocarinoma. **Possible adverse effect:** increased incidence of thyroid tumors; **Chronic NOEL:** (M/F) 400 ppm ((M) 17 mg/kg/day, (F) 22 mg/kg/day) (based upon the treatment-related effects in the liver and thyroid glands of the 5000 ppm treatment group); **Possible**

carcinogen: increased incidence of thyroid tumors. **Study acceptable.** (Moore, 1/27/05)

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

** 0148, 0149; 205784, 205785; "Technical SN 100309: Dog 12 Month Oral (Gavage) Repeat Dose Study"; (S.J. Rees; Schering Agrochemicals Limited, Chesterford Park, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81809; 11/11/92); Four beagle dogs/sex/group were dosed orally by gavage with 0, 2, 30, or 400 mg/kg/day of Technical SN 100 309 (code/batch no. CR 19325/4; purity: 96.3% (7/30/90), 96.8% (12/17/91) in aqueous methylcellulose (0.5% (w/v)) for 12 months. The dose for the 400 mg/kg group was adjusted to 250 mg/kg/day after 7 days of treatment due to excessive vomiting (4 males, 3 females). The mean body weights and food consumption for both sexes in the 400/250 mg/kg group were lower than those values of the control through out the study. There were no apparent treatment-related effects evident in the hematology, urinalysis or ophthalmological evaluations. The total bilirubin levels in the serum for both sexes in the 400/250 mg/kg group was lower than those of the control group at various times during the study ($p<0.05$ or 0.01). No treatment-related effects were noted for the organ weights in the necropsy examination. No treatment-related lesions were apparent in the histopathological evaluation. **No adverse effect indicated. Chronic NOEL:** (M/F) 30 mg/kg/day (based upon the clinical signs and lower mean body weights and food consumption noted for the animals in the 400/250 mg/kg group); **Study acceptable.** (Moore, 1/28/05)

ONCOGENICITY, RAT

See Combined Rat, above.

ONCOGENICITY, MOUSE

** 0150 to -0153; 205786, 205787, 205788, 205789; "Technical SN 100309: 80 Week Oral (Dietary Administration) Carcinogenicity Study in the Mouse"; (H. Clay, G. Healing; Hazleton UK, Harrogate, North Yorkshire, England; Report No. A81811; 3/31/93); Fifty one CD-1 mice/sex/group received 0, 16, 160 or 1600 ppm of Technical SN 100 309; batch no. CR 19325/4; purity: 96.0% (5/29/90), 97.3% (5/8/92) in the diet for 80 weeks ((M) 0, 2.0, 20.0, 210.9 mg/kg/day, (F) 0, 2.5, 24.9, 253.8 mg/kg/day). There was no treatment-related effect upon the mean body weights and food and water consumption. The differential white blood cell count did not demonstrate any apparent treatment-related effect. Mean absolute or relative organ weights were not affected by the treatment. In the histopathology examination, there was an increase in the incidence of urogenital tract lesions noted as the cause of death for the males in the 1600 ppm group (0: 3/17 vs. 16: 9/29, 160: 5/16, 1600: 12/21). **No adverse effect indicated. Chronic Dietary NOEL:** (M) 160 ppm (20.0 mg/kg/day) (based upon an increased incidence of urogenital tract lesions for the 1600 ppm males) (F) 1600 ppm (253.8 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose tested); **Oncogenicity not evident. Study acceptable**. (Moore, 2/2/05)

REPRODUCTION, RAT

** 0154, 0155; 205790, 205791; "Technical SN 100309: Two Generation Oral (Dietary Administration) Toxicity Study in the Rat"; (R. Clark; Hazleton UK, Harrogate, North Yorkshire, England; Report No. A81822; 3/31/93); In the P generation, 30 Sprague-Dawley rats/sex/group received 0, 32, 400 or 5000 ppm of Technical SN 100 309 (batch no. CR19325/4, purity: 96.9% (10/5/90), 96.2% (11/28/91)) in the diet for a 14 week premating period, mating and 3 week intervals for gestation and lactation. Twenty five animals/sex/group in the F1 generation were dosed in the same manner from the time of weaning through a 15 to 16 week premating interval, mating and 3 week intervals for both gestation and lactation of the F2 generation. No apparent treatment-related deaths occurred during the study. The mean body weight gain and food consumption of both sexes in the 5000 ppm group for both generations were less than those values of the controls (NS to $p<0.001$). There was no treatment-related effect upon any of the reproduction indices for either generation. The mean body weights of the 5000 ppm pups

throughout the lactation period of both generations were less than those of the controls ($p<0.001$). There was no treatment-related effect upon the viability of the pups in either generation. In the functional tests for the pups, the day 17 assessment of the air righting reflex indicated a slight affect on the 5000 ppm animals in both generations. Otherwise, no treatment-related effects were noted in the other functional tests or in the physical development criteria of pinna unfolding, incisor eruption or eye opening. **No adverse effect indicated. Parental NOEL:** (M/F) 400 ppm ((M) 18.4 to 53.2 mg/kg/day, (F) 23.4 to 73 mg/kg/day) (based upon the reduced body weight gain and food consumption demonstrated by the animals in the 5000 ppm treatment group of both generations; **Reproduction NOEL:** 5000 ppm (((M) 238.9 to 418.3 mg/kg/day, (F) 294.4 to 1353 mg/kg/day) (based upon the lack of effect on reproduction indices at the highest dose tested); **Developmental NOEL:** 400 ppm ((M) 18.4 to 53.2 mg/kg/day, (F) 23.4 to 73 mg/kg/day) (based upon the lower mean body weights of the pups in the 5000 ppm group of both generations); **Study acceptable.** (Moore, 2/8/05)

TERATOLOGY, RAT

** 0156, -0157, 205792, 205793; "Technical SN 100309: Rat Oral Developmental Toxicity (Teratogenicity) Study; (C.M. Jackson, L.K. Bennett; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81800; 11/4/91); Thirty time-mated female Sprague-Dawley rats/group were dosed orally by gavage with 0 (aqueous 1% (w/v) methyl cellulose), 7, 85 or 1000 mg/kg/day of Technical SN 100 309 (batch no. CR19325/4; purity: 96.3% (7/30/90)), 97.0% (10/9/90)) from day 6 through day 15 of gestation. One female each in the control and 7 mg/kg groups died during the study for reasons unrelated to the test material. The mean body weights and food consumption of the 1000 mg/kg dams were less than those of the controls ($p<0.001$ and $p<0.05$, respectively). The mean body weight of the fetuses in the 1000 mg/kg group was less than that of the controls ($p<0.01$). Otherwise, there were no apparent treatment-related effects on any of the litter parameters or the incidence of fetal abnormalities. **No adverse effect indicated. Maternal NOEL:** 85 mg/kg/day (based upon the lower mean body weights and food consumption of the 1000 mg/kg days); **Developmental NOEL:** 85 mg/kg/day (based upon the lower mean body weight of the fetuses in the 1000 mg/kg group); **Study acceptable.** (Moore, 2/9/05)

0158; 205794; "Technical SN 100309: Rat Oral Developmental Toxicity (Teratogenicity) Range-Finding Study (Chernoff Kavlock Assay); (C.M. Jackson, L.K. Bennett; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81804; 1/6/92); Six female time-mated Sprague-Dawley rats/group were dosed orally by gavage with 0 (1% w/v aqueous methyl cellulose), 500 or 1000 mg/kg/day of Technical SN 100 309 (batch no. CR19325/3, purity: 97.8% (3/9/90)) from day 6 through day 15 of gestation. Two dams, one in the control group and the other in the 1000 mg/kg group died on gestation day 9 due to apparent dosing errors. The body weight gain for the 1000 mg/kg dams was less than that observed for the control animals over the dosing period. There was no treatment-related effect noted for the offspring through 7 days post-natal. No external abnormalities were evident. **No adverse effect indicated. Study supplemental.** (Moore, 2/8/05)

TERATOLOGY, RABBIT

** 0159, -0160; 205795, 205796; "Technical SN 100309: Oral (Gavage) Development Toxicity (Teratogenicity) Study in the New Zealand White Rabbit"; (L.F.H. Irvine; Toxicol Laboratories Limited, Ledbury, Herefordshire, HR8 1LH, England; Report No. Tox 90476; 1/15/91); Eighteen or nineteen time-mated female New Zealand White rabbits/group were dosed orally by gavage with 0 (aqueous 1% methyl cellulose), 7, 45 or 300 mg/kg/day of Technical SN 100 309 (batch no. CR 19325/3, purity: 97.1%) from day 7 through day 19 of gestation. Three does in the 300 mg/kg group were euthanized *in extremis* on days 15, 22 and 24 of gestation. The mean body weight gain value of the does in the 300 mg/kg group during the first 2 days of dosing was less than that of the control group ($p<0.01$). The mean food consumption of the 300 mg/kg does was less than that of the control group throughout the dosing period ($p<0.001$). The mean weight of the fetuses in the 300 mg/kg group was less than that of the controls ($p<0.01$). Otherwise, no effects on the fetal development were noted. **No adverse effect indicated. Maternal NOEL:** 45 mg/kg/day

(based upon the reduced mean weight gain and food consumption of the 300 mg/kg/day); **Developmental NOEL:** 45 mg/kg/day (based upon the lower mean body weights of the fetuses in the 300 mg/kg/day group); **Study acceptable.** (Moore, 2/14/05)

0161; 205797; "Technical SN 100309: Oral (Gavage) Rabbit Teratology Dose Ranging Study"; (L.F.H. Irvine; Toxicol Laboratories Limited, Ledbury, Herefordshire, HR8 1LH, England; Report No. TOX 89310; 1/15/91); Three preliminary dose range-finding studies were performed. In the first study, 3 non-mated female New Zealand White rabbits were dosed orally by gavage over 15 days with Technical SN 100 309 (batch no. CR 19325/1, purity: 99.2%). For days 1 to 3, they received 50 mg/kg/day. From days 4 to 6, the dose was increased to 100 mg/kg/day. The dose was further increased to 200 mg/kg/day for days 7 to 9, to 400 mg/kg/day for days 10 to 12 and to 800 mg/kg/day for days 13 to 15. In the second study, 3 non-mated females were dosed with 800 mg/kg/day for 5 days. Dosing was discontinued for 3 days and then resumed for another 3 days at 500 mg/kg/day. In the 3rd study, 5 time-mated females/group were dosed with 0 (1% aqueous methyl cellulose) 50, 250 or 500 mg/kg/day of the test material for days 7 through 19 of gestation. The animals in the 1st study demonstrated slight reduction in body weight and food consumption at 400 mg/kg/day and body weight loss and marked reduction in food and water consumption at 800 mg/kg/day. In the necropsy examination, pitted kidneys and ulceration of the stomach mucosa were noted. In the 2nd study, the treatment at 800 mg/kg/day resulted in body weight loss and marked reduction in food and water consumption. When dosing was resumed after a 3 day interlude at 500 mg/kg/day, one of the 3 females died after 2 doses and the other two exhibited marked reduction in food and water consumption. Ulceration of the stomach mucosa, a pale kidney and an abnormal bladder were noted in the necropsy examination of the deceased animal. In the 3rd study, all of the animals survived the treatment period. One of the 500 mg/kg females aborted on day 19. A dose-related effect on body weights was noted for all of the treatment groups (the 50 mg/kg group lost weight on the 1st two days of dosing and then gained in a manner similar to the controls). Food consumption was affected in a similar dose-related manner. Examination of the fetuses for the treated dams did not reveal any apparent treatment-related effects. **No adverse effect indicated. Study supplemental.** (Moore, 2/14/05)

GENE MUTATION

** 0117; 205743; "Technical SN 100 309: *In Vitro* Chinese Hamster Ovary/HPRT Locus Gene Mutation Assay"; (K. Adams, S. Henly, A. Godfrey; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. TOX 91169; 8/20/92); Chinese Hamster Ovary cells (CHO-K1-BH_4) were exposed to concentrations of Technical SN100309 (batch no. CR 19325/01/900304, purity: 97.2%) ranging from 10 to 400 ug/ml for 4 hours at 37° C under conditions of activation and non-activation in the 1st trial. In the 2nd trial, the cells were exposed under the same conditions to concentrations which ranged from 10 to 240 ug/ml under non-activated conditions and from 10 to 280 ug/ml under conditions of activation. Duplicate cultures were performed for each treatment level. The S9 fraction used to metabolize the test material was derived from the livers of male Sprague-Dawley rats pretreated with Aroclor 1254. An increased rate of mutation was not consistently demonstrated at any treatment level with or w/o activation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 12/3/04)

** 0140; 205776; "Technical SN 100 309: Bacterial Mutation Assay"; (E. Jones, R.A. Gant; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. TOX 89279; 3/25/90); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to Technical SN 100 309 (batch no. CR19325/1, purity: 98.7%) at concentrations ranging from 15 to1500 ug/plate for 30 minutes at 37° during a pre-incubation period followed by exposure for 72 hours at 37° C, using the plate incorporation technique, under conditions of non-activation and activation. Two trials were performed with 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 1/18/05)

** 0141; 205777; "Technical SN 100309: Bacterial Mutation Assay with *Escherichia coli";* (E. Jones, R.A. Gant; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England*;* Study No. TOX 91109; 9/2/91); *E. coli* strains CM 881 WP2 trp uv resistant pKM 101 and CM 891 WP2 trp *uvr*A pKM 101 were exposed to Technical SN 100 309 (batch no. CR 19325/01/900304, purity: 96.4%) at concentrations ranging from 15 to 1500 ug/plate for 72 hours at 37^{o} C under conditions of non-activation and activation. Two trials were performed with 3 plates per treatment level. An S9 fraction derived from the liver of rats pretreated with Aroclor 1254 was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation to tryptophan independence. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 1/18/05)

CHROMOSOME EFFECTS

** 0142; 205778; "Technical SN 100309: Metaphase Chromosome Analysis of Human Lymphocytes Cultured *in Vitro*"; (P.C. Brooker, L.C. Akhurst, J.D. King, A. Howell; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. Tox 90223; 7/19/90); Primary human lymphocyte cultures, procured from the whole blood of volunteers (stimulated with PHA for 48 hours), were treated with 1.0 to 500 ug/ml of Technical SN 100 309 (batch no. CR 19325/3, purity: 97.4%) for 24 or 42 hours under conditions of non-activation and for 2 hours followed by incubations of 22 or 40 hours under conditions of activation. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. No treatment-related increase in chromosomal aberrations was evident in the assay. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 1/19/05)

DNA DAMAGE

** 0143; 205779; "Technical SN 100309: Unscheduled DNA Synthesis Assay in Rat Hepatocytes Treated *in Vivo*"; (R.J. Proudlock, W.R. Howard; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. TOX 90226; 6/21/91); Eight Sprague-Dawley male rats/group received a single oral dose of 0 (1% aqueous methylcellulose), 100, 300 or 1000 mg/kg of Technical SN 100 309 (batch no. CR 19325/4, purity: 97.6%) by gavage. Hepatocytes from 3 animals/group/time point were isolated at 2 and 14 hours post-dosing. Viability was determined by trypan blue dye exclusion and ranged from 73% to 99%. After attachment, cells were exposed to (methyl-^{3}H) thymidine for 4 hours followed by 24 hours with unlabelled thymidine. Three replicate cultures were performed per animal. Three slides per animal were scored, 50 cells per slide. No increase in the net nuclear grain counts was evident at any dose level or sampling time. **No adverse effect indicated**. Positive control was functional. **Study Acceptable**. (Moore, 1/19/05).

** 0144; 205780; "Technical SN 100309: Mouse Micronucleus Test"; (R.J. Proudlock; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Study No. TOX 90501; 5/13/91); Fifteen CD1 mice/sex/group were dosed orally by gavage with 0 (1% CMC), 225, 450 or 900 mg/kg of Technical SN 100 309 (batch no. CR 19325/4, purity: 97.6%). An additional 5 animals/sex/group were dosed with either 900 mg/kg of the test material or 12 mg/kg of Mitomycin C. Five animals/sex/time point were euthanized at 24, 48 and 72 hours post-dose except for the positive control animals which were euthanized at 24 hours. One female in the 900 mg/kg group died. Animals in all of the treatment groups demonstrated hunched posture, and piloerection. The animals in the two higher dose groups exhibited lethargy and the animals in the 900 mg/kg group had a decreased respiratory rate. Some of the animals in this high dose group also were in a comatose state. The incidences of micronucleated polychromatic (PCE) and normochromatic (NCE) erythrocyctes and the ratio of PCEs to NCEs were reported. There was no treatment-related increase in the percentage of micronucleated PCEs. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 1/21/05)

NEUROTOXICITY

Acute Neurotoxicity, Rat

52950-0118; 205744; "A Time to Peak Behavioral Effects Study of Pyrimethanil Technical in the Rat"; (P. Beyrouty; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Project ID. 97572; 8/22/01); Three Sprague-Dawley rats/sex/group were dosed orally by gavage with 0

(aqueous 0.5% methyl cellulose), 500, 1000 or 2000 mg/kg of Pyrimethanil technical (lot No. 14/00, purity: 99.8%). No deaths resulted from the treatment. Functional assessments of the animals were performed prior to dosing and at 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post dose. Ataxia, reduced respiration and lowered body temperature were noted as apparent treatment-related effects. The time for peak effect for ataxia was one to two hours, for reduced respiration, 1.5 to 2 hours and for lowered body temperature, 2 to 4 hours post-dose. **Possible adverse effect:** impaired gait. **Supplemental Study.** (Moore, 12/6/04)

52950-0119; 205745; "An Acute Oral Neurotoxicity Study of Pyrimethanil Technical in Rats"; (P. Beyrouty; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Project ID. 97567; 9/24/01);
Twelve Sprague-Dawley rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% methyl cellulose), 30, 100 or 1000 mg/kg of Pyrimethanil technical (lot no. 14/00; purity: 99.8%). No deaths resulted from the treatment. In the Functional Observational Battery (FOB), both sexes in the 1000 mg/kg group demonstrated slight or moderate ataxic and overall gait incapacity at 1.5 - 2 hours post-dose ($p<0.01$ or $p<0.001$). A number of females in the 1000 mg/kg group also demonstrated moderately dilated pupils at this time point ($p<0.05$). Lower mean body temperatures were also noted for both sexes in the 1000 mg/kg group ($p<0.001$) and for the males in the 100 mg/kg group ($p<0.05$) on the 1st day. The hindlimb grip strength for the 1000 mg/kg males was less than that of the control on the 1st day ($p<0.001$). The mean activity counts for both sexes in the 1000 mg/kg group ($p<0.001$) and for the males in the 100 mg/kg group (NS) were lower than those of the control on the 1st day. The females in the 1000 mg/kg group demonstrated increased urination on day 8 of the study ($p<0.001$). However, this was the only time this sign was noted and therefore was not considered to be treatment related. No treatment-related lesions were evident in the neuropathological evaluation. **Possible adverse effect:** impairment of gait. Reported **Acute Neurotoxicity NOEL:** (M) 30 mg/kg, (F) 100 mg/kg (based upon lower mean body weight temperatures for the 100 mg/kg males and for the 1000 mg/kg females). **Study unacceptable**, possibly upgradeable to acceptable with the submission of positive control data which document the competence of the laboratory staff to perform the FOB. (Moore, 12/7/04)

Rat Subchronic Neurotoxicity Study

52950-0120; 205746; "A 13-Week Dietary Neurotoxicity Study of Pyrimethanil Technical in Rats"; (P. Beyrouty; ClinTrials BioResearch Ltd., Senneville, Quebec, Canada; Project ID. 97568; 10/19/01); Twelve Sprague-Dawley rats/sex/group received 0, 60, 600 or 6000 ppm of Pyrimethanil technical (lot no. 14/00; purity: 99.8%) in the diet for 13 weeks ((M) 0, 4.0, 38.7, 391.9 mg/kg/day, (F) 0, 4.4, 44.3, 429.9 mg/kg/day). No deaths resulted from the treatment. The mean body weights for both sexes in the 6000 ppm treatment group were lower than those of the control animals throughout the study ((M): NS, (F) $p<0.05$, day 92). The mean food consumption for the high dose animals was lower than that of the controls during the 1st 5 days of the study ($p<0.01$). The food consumption recovered for these animals in succeeding weeks. There were no treatment-related effects evident in the FOB or motor activity assessments throughout the 13 week study period. There were no treatment-related lesions noted in the histopathological evaluation. **No adverse effect indicated.** Reported **Subchronic Dietary NOEL:** (M/F) 600 ppm (M: 38.7 mg/kg/day, F: 44.3 mg/kg/day) (based upon lower mean body weight and food consumption for the animals in the 6000 ppm treatment group); **Study unacceptable**, possibly upgradeable to acceptable with the submission of positive control data which document the competence of the laboratory staff to perform the FOB. (Moore, 12/17/04)

METABOLISM STUDIES

Metabolism, Rat

0162; 205798; " Residue Levels in Rat Tissues Following Repeated Daily Oral Dosing with [^{14}C] SN 100 309 at 10 mg/kg Bodyweight"; (P.A. Hemmings; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81622; 7/25/91); Males Sprague-Dawley rats were dosed orally by gavage once per day for up to 28 days with 10 mg/kg/day of [^{14}C] SN 100 309 (batch no. 2331-3/A, specific activity: 119 uCi/mg; purity: >98%, SN 100 309 technical, batch no. CR19325/4, purity: >99%) (3 uCi/mg, final

specific activity). Three animals/time point were euthanized after 1, 3, 5, 8, 11, 17, 23, and 28 days of treatment. A final group of 3 received 28 doses and then were euthanized 96 hours after the last dose. Although the protocol stated that urine and feces were collected over this 96 hour period, no results were included in the report. Radiolabel was recovered from liver at every time point assayed. The concentration of the radiolabel was found to increase over the course of the treatment in the liver, kidneys, blood, adrenals and thyroid. Only on the 28th day was any label found in the spleen. Ninety six hours after the cessation of dosing, radiolabel was recovered from the kidney, liver, and thyroid. **Study supplemental.** (Moore, 2/15/05)

0163; 205799; "The Distribution and Excretion of Radiolabelled Residues in the Rat Following Oral Dosing with SN 100 309 at 11.8 or 800 Mg/kg Bodyweight"; (D. Needham, P.A. Hemmings; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81623; 8/22/91); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 11.8 mg/kg of [^{14}C]-SN 100 309 (batch no. 2331-3, specific activity: 119 mCi/mg, radiochemical purity: >99%; SN 100 309 technical, batch no. CR 19298/1, purity: 99.4%;) or 800 mg/kg of [^{14}C]-SN 100 309 (batch no. 2331-6, 141 uCi/mg, radiochemical purity: >98%; SN 100 309 technical, batch no. CR 19325/1, purity: >98%). Urine and feces were collected daily over a 96 hour period post-dose. The distribution of radiolabel in the tissues was assessed at the end of this time period. The primary route of excretion was in the urine with 74 to 76% and 65 to 67% of the administered radiolabel recovered in the urine of the low and high dose animals, respectively. An additional 5 to 6% and 12 to 15% of the label was found in the cage wash of the respective dose groups. Recovery in the feces ranged from 15 to 23% of the administered dose. For the low dose animals, the 95 to 98% of the radiolabel was excreted in the first 24 hours. The rate of excretion was lower in the high dose group with 63 to 67% of the radiolabel recovered in the first 24 hours. In the low dose group, the liver was the only organ for which radiolabel was recovered at 4 days post-dose. In the high dose group radiolabel was recovered from multiple tissues with the liver, kidneys, blood, and thyroid demonstrating the highest levels of label. **Study supplemental.** (Moore, 2/15/05)

0164; 205800; "SN 100 309: Metabolism in the Rat"; (D. Needham, P.A. Hemmings; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81626; 8/2/93); The radiolabeled metabolites which had been recovered in the urine and feces of male and female Sprague-Dawley rats treated with either single doses of radiolabeled SN 100 309 at doses of 11.8 or 800 mg/kg or pretreated with 10 mg/kg/day of unlabeled SN 100 309 for 14 days followed by treatment with 10 mg/kg of radiolabeled SN 100 309
(see vol. nos. 52950-0163, -0165, rec. nos. 205799, 205801) were isolated and identified. The primary pathway of metabolism was the hydroxylation of either of the aromatic rings or the methyl groups attached to the pyrimidyl ring. A significant fraction of the recovered radioactivity consisted of polar metabolites which appeared to be polymers of the various phenolic metabolites. Use of the multiple dosing regimen resulted in an increasing percentage of the recovered radioactivity present in this polar fraction. There was a corresponding decrease in the recovery of SN 614 276 in both the urine and the feces. **Study supplemental.** (Moore, 2/24/05)

0165; 205801; "SN 100 309: Excretion and Tissue Residues of a Radiolabelled Oral Dose in Rats Following Pre-Dosing for 14 Days with Unlabelled SN 100 309"; (P.A. Hemmings; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron, Walden, Essex CB10 1XL, Great Britain; Report No. A81631; 5/21/93); Five Sprague-Dawley rats/sex were dosed orally by gavage with 10 mg/kg/day of unlabeled SN 100 309 technical for 14 days followed by a single dose of 10 mg/kg of [^{14}C]-SN 100 309 (batch no. 2331-6, specific activity: 141 uCi/mg, radiochemical purity: >99%; SN 100 309 technical, batch no. CR 19325/01/900304, purity: 99.4% (final specific activity: 2.6 uCi/mg). Urine and feces were collected at 6 and 24 hours post-final dose. Urine was the predominant path of excretion with 59 to 62% of the administered dose being recovered within the first 24 hours. An additional 10 to 14% was recovered in the cage wash. Seventeen to 18% of the administered dose was recovered in the feces. One to two percent of the administered radiolabel was recovered in the gastrointestinal tract at 24 hours post-

final dose. The blood, kidneys and liver were the only tissues from which radioactivity was recovered. **Study supplemental**. (Moore, 2/16/05)

The four rat metabolism studies are supplemental. However, the combined information provided by these study data are sufficient to assess the pharmacokinetics and metabolic profile of this active ingredient.

SUBCHRONIC STUDIES

Rat 7-Day Dietary Thyoid Function Test

52965-0132; 205761; "Technical SN 100 309: Rat 7-Day Dietary Thyroid Function Test Using Perchlorate Discharge as a Diagnostic Test"; (G. Healing; Schering Agrochemicals Ltd., Chesterford Park Research Station, Saffron, Walden, Essex, CB10 1XL, England; Report No. TOX/92/223-55; 11/12/92); Twelve male Sprague-Dawley rats/group received 0 or 5000 ppm of Technical SN 100 309 (code/batch no. CR 19325/01/900304, purity: 96.2%) in the diet for 7 days 509 mg/kg/day). An additional 2 groups of 12 males/group received either 2000 ppm of propyl thiouracil (177 mg/kg/day) or 1000 ppm of phenobarbital (109 mg/kg/day) in the diet for the same time period. Six hours prior to being euthanized, each rat was injected ip with 1 uCi of ^{125}I. At 2.5 minutes prior to euthanasia, 6 rats in each group were injected ip with either 10 ml/kg of physiological saline or 10 mg/kg of potassium perchlorate in physiological saline. The thyroid glands were excised and the radioactivity in the blood and thyroid samples was measured in a gamma radiation counter. The total thyroid count, blood count, thyroid weight, and blood volume were used to calculate a thyroid to blood ^{125}I ratio. Treatment with perchlorate is used to enhance the discharge from the thyroid of any non-bound iodine which may have built up due to the inhibition of thyroidal peroxidase enzymes. The mean body weight and food consumption values of the SN 100 309 treated animals were lower than those of the control group during the first 4 days of the treatment ($p<0.05$). The results of treatment with SN 100 309 demonstrated a similar effect on iodine distribution as was noted for the phenobarbital treated animals. The thyroid was apparently affected by induction of liver enzymes which enhanced the metabolism of thyroid hormones. **Possible adverse effect:** thyroid toxicity; **Supplemental study**. (Moore, 1/5/05)

Rat 14-Day Dietary Toxicity Study

52950-0131; 205760; "Technical SN 100 309: Rat 14-Day Dietary Study to Investigate the Mechanism of Thyroid Response"; (G. Healing; Schering Agrochemicals Ltd., Chesterford Park Research Station, Saffron, Walden, Essex, CB10 1XL, England; Report No. TOX/92/223-56; 11/12/92); Ten male Sprague-Dawley rats/group received 0 or 5000 ppm of Technical SN 100 309 (code/batch no. CR 19325/01/900304, purity: 96.2%) in the diet for 14 days (0, 378.5 mg/kg/day). Five animals/group were euthanized on day 15 and the remaining 5 animals/group were euthanized on day 29 after a 2 week recovery period. No deaths resulted from the treatment. The mean body weight and food consumption values of the 5000 ppm males were less than those of the control group during the 1st week of the study ($p<0.05$). During the 2 week treatment period, the mean serum triiodothyronine (T3) and thyroxine (T4) levels were generally less than those of the control (NS or $p<0.05$ or 0.01). The mean serum thyrotropin (TSH) levels were elevated during this period (NS or $p<0.05$ or 0.01). No treatment-related effects on these parameters were evident by day 29. The hepatic uridine diphosphoglucuronyl transferase activity level for the 5000 ppm animals after 14 days of treatment was greater than that of the control ($p<0.001$). After the 2 weeks recovery, the activity had largely returned to the control level. The mean absolute and relative liver weights for the 5000 ppm animals were greater than those of the control after 14 days ($p<0.05$ or 0.01), returning to the control values after the 2 week recovery. The mean absolute and relative thyroid weights were lower than those of the controls both after 14 days of treatment and the 2 week recovery period ($p<0.01$). In the histopathology examination, an increased incidence of centrilobular hepatocyte enlargement was evident in the liver after 14 days of treatment (0: 1/5 vs. 5000: 5/5). This effect was not evident after the recovery period. A more severe incidence of colloid depletion was evident in the thyroid gland of the 5000 ppm animals than that of the controls after 2 weeks of treatment with the effect ranging from moderate to severe. This effect was still evident after the recovery period with a more moderate response being noted. Follicular epithelial hyperplasia was also noted in the treated

animals after the treatment (0: 1/5 vs. 5000: 4/5) with the effect still somewhat evident after the recovery period (0: 0/5 vs. 5000: 2/5). The author of the report surmised that the effect on the thyroid was attributable to the enhanced metabolism of the thyroid hormones by the induced liver enzymes which resulted in an increased secretion of TSH by the pituitary gland. **Possible adverse effect:** thyroid gland toxicity; **Subacute NOEL (M):** < 5000 ppm (378.5 mg/kg/day); **Study supplemental.** (Moore, 1/4/05)

Rat 28-Day Dietary Toxicity Study

52950-0115; 205741; "Technical SN 100 309: 28-Day Dietary and Repeated Dose Study in Rats"; (P.W. Harvey; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron Walden, Essex CB10 1XL, Great Britain; Report No. TOX/89/223-10; 1/16/91); Five Sprague-Dawley rats/sex/group received 0, 10000, 15000, or 30000 ppm of Technical SN 100 309 (code/batch no. CR 19325/1, purity: 99.2% (9/89)) in the diet for 28 days ((M) 0, 844, 1135, 2434 mg/kg/day, (F) 0, 844, 1187, 2967 mg/kg/day). An additional group of 5 animals/sex were dosed orally by gavage with 1500 mg/kg/day of the test material for 11 days, followed by dosing with 1000 mg/kg/day for the remaining 17 days. In the 1500 mg/kg gavage group, one male and 3 females died or were euthanized *in extremis* by day 15. At least three of the animals were considered to have suffered dosing accidents. One or more animals in the 30000 ppm group demonstrated signs of reduced activity, unsteady gait, soiling of the urogenital region, reduced muscle tone, hunched posture, and emaciation. One or more animals in the 10000 ppm group exhibited signs of emaciation and facial soiling. In the 1500/1000 mg/kg group, the clinical signs were much the same as those observed for the 30000 ppm group. The mean body weights of both sexes in the 10000 ppm group and above were less than those of the controls ($p<0.05$ or NS). The mean food consumption of the treated groups in the dietary study was reduced in a dose related manner. In the hematology examination, increased red blood cell counts and hemoglobin levels were noted for both sexes in the 30000 ppm treatment group, possibly as a consequence of the severe body weight loss experienced by the animals in this group. In the clinical chemistry evaluation, the blood urea nitrogen levels were increased for both sexes in the 30000 ppm group ($p<0.01$). The total bilirubin concentrations were increased for the females in the 15000 ppm group and for both sexes in the 30000 ppm group ($p<0.05$ and $p<0.001$). The gamma-glutamyl transpeptidaase activity levels in the serum were elevated for both sexes in the 15000 ppm and 30000 ppm groups ($p<0.05$ and $p<0.01$). The alkaline phosphatase activity levels were elevated for the males in the 10000 and 15000 ppm groups and for the females in the 30000 ppm group ($p<0.05$ or $p<0.01$). In the necropsy examination, the mean relative liver weights for all of the treatment groups were greater than those of the control ($p<0.01$). The mean relative kidney weights for the 15000 ppm females and for both sexes in the 30000 ppm group were greater than those of the controls ($p<0.05$). In the histopathological examination, the target organ for the animals receiving the test material in the diet was the kidney. Tubular dilatation, tubular necrosis and karyomegaly in the tubular epithelium were evident for the males (dilatation: 0: 0/5 vs. 10000: 1/5 and 30000: 3/5; necrosis: 0: 0/5 vs. 30000: 2/5; karyomegaly: 0: 0/5 vs. 30000: 2/5). Testicular tubular atrophy was also noted in the males of the 30000 ppm group (0: 0/5 vs. 30000: 2/5). The esophagus and thyroid gland were target organs for the males receiving the gavage doses. Focal acute inflammation was noted in the esophagus (4/5). In the thyroid, colloid depletion (5/5), agglomeration of colloid (3/5), follicular cell hypertrophy (5/5) and follicular epithelial cell hyperplasia (5/5) were evident. For the females receiving the dietary treatment, the kidney was the target organ with tubular dilatation (0: 0/5 vs. 10000: 1/5, 15000: 2/5, 30000: 5/5), basophilic tubules (0: 0/5 vs. 10000: 1/5, 15000: 3/5, 30000: 5/5), tubular necrosis (0: 0/5 vs. 10000: 1/5, 15000: 3/5, 30000: 5/5), increased mitotic divison in the tubular epithelium (0: 0/5 vs. 30000: 4/5), karyomegaly in tubular epithelium (0: 0/5 vs. 30000: 5/5) and lymphocytic infiltration (0: 0/5 vs. 30000: 3/5) being noted. For the females receiving the gavage doses, focal acute inflammation of the esophagus (3/5) and diffuse epithelial hyperplasia of the fore stomach (3/5) was noted. In the thyroid gland, colloid depletion (2/5), agglomeration of colloid (2/5) and follicular cell hypertrophy (2/5) was reported. Note that for these females, three of them had died by the end of the 2nd week of the study. **Possible adverse effect:** renal tubular necrosis; **Subacute Dietary NOEL:** (M/F) < 10000 ppm ((M/F) < 844 mg/kg/day) (based upon reduced mean body weights, increased mean relative liver weights for both sexes in the 10000 ppm group

and for the renal lesions noted for the females in the 10000 ppm group). **Study supplemental.** (Moore, 11/30/04)

Rat Subchronic Dietary Toxicity Study

52950-0133, -0134, -0135; 205769, 205770, 205771; "Technical SN 100 309: 13 Week Oral (Dietary) Toxicity Study in the Rat Followed by a 4 Week Regression Period"; (A.T. Higham; Schering Agrochemicals Ltd., Chesterford Park Research Station, Saffron, Walden, Essex, CB10 1XL, England; Report No. A81783; 11/13/90, amendment, 10/5/92); Ten Sprague-Dawley rats/sex/group received 0, 80, 800 or 8000 ppm of Technical SN 100 309 (code/batch no. CR 19325/2, purity: 98.1% (9/14/89), 95.6% (12/4/89), 95.3% (6/21/90)) in the diet for 13 weeks ((M) 0, 5.4, 54.5, 529.1 mg/kg/day, (F) 0, 6.8, 66.7, 625.9 mg/kg/day). An additional 10 animals//sex/group received 0 or 8000 ppm of the test material in the diet and then were maintained for a 4 week recovery period. One control male was euthanized *in extremis* on day 46. A second control male died during blood sampling due to an accidental ether overdose. Both sexes in the 8000 ppm treatment group demonstrated lower mean body weight and food consumption during the treatment period. Although food consumption was comparable between the control and treated groups during the recovery period, the mean body weights were still lower for the 8000 ppm animals in comparison to the control at the end of the 4 week recovery period. No treatment-related effects were evident in the hematology, clinical chemistry, urinalysis or ophthamology assessments. The mean relative liver and kidney weights were greater for both sexes in the 8000 ppm treatment group ($p<0.01$ or 0.001). These effects were no longer evident in the recovery animals. In the histopathological examination, hepatocellular hypertrophy was noted in the liver of the 800 and 8000 ppm males (0: 0/10 vs. 800: 2/10, 8000: 9/10). For the females, one animal in the 8000 ppm group exhibited hepatocellular hypertrophy. No apparent treatment-related effect was evident in the recovery animals. In the thyroid gland, there was an increased incidence of follicular cell epithelial hypertrophy in both sexes of the 8000 ppm group ((M) 0: 3/10 vs. 8000: 9/10, (F) 0: 0/10 vs. 8000: 6/10). The incidence of the effect was comparable for both sexes in both groups after the recovery. The presence of brown pigment in the thyroid epithelium was noted in both sexes in the 8000 ppm group ((M) 0: 0/10 vs. 8000: 8/10, (F) 0: 0/10 vs. 8000: 7/10) which persisted somewhat through the recovery period ((M) 0: 0/10 vs. 8000: 2/10, (F) 0: 0/10 vs. 8000: 2/10). Depletion of thyroid colloid was noted for the 8000 ppm females (0: 0/10 vs. 5/10). The incidence of the effect was comparable for both sexes in both groups after the recovery. **Adverse effect:** toxic effect on the thyroid. **Subchronic NOEL:** (M) 80 ppm (5.4 mg/kg/day) (based upon the incidence of hepatocyte hypertrophy noted for the 800 ppm males), (F) 800 ppm (66.7 mg/kg/day) (based upon reduced mean body weight and food consumption and increased mean relative liver weights and the thyroid effects noted for the 8000 ppm females). **Study acceptable.** (Moore, 1/10/05)

Dog 28-Day Oral Toxicity Study

52950-0116; 205742; "Technical SN 100 309: 28-Day Repeat Dose Study in Dogs"; (P.W. Harvey, M. Davies; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron Walden, Essex CB10 1XL, Great Britain; Report No. TOX/89/223-2; 10/22/90); Two beagle dogs/sex/group were dosed orally by intubation with 0, 100, 500 or 1000 mg/kg/day of Technical SN 100 309 (code/batch no. CR 19325/1, purity: 99.0% (7/89)) for 28 days. After 6 days of treatment, the high dose level was reduced to 800 mg/kg/day due to the frequent vomiting of these study animals. No deaths occurred during the study. Clinical signs included the increased frequency of vomiting and salivation among the high dose animals. The mean body weight gain and food consumption of the high dose females were less than those of the control animals during the first week of the treatment. There were no treatment-related effects noted in the hematology, ophthalmology or urinalysis evaluations. The mean serum cholesterol levels were greater for both sexes in the high dose group than those of the controls over the course of the study. The mean
absolute and relative liver weights of the high dose females were greater than those of the controls. The histopathological examination did not reveal any apparent treatment-related lesions. **No adverse effect indicated. NOEL:** not determined due to the limited number of study animals which were included in the study. **Study supplemental.** (Moore, 12/1/04)

Dog Subchronic Oral Toxicity Study

52950-0138, -0139; 205774, 205775; "Technical SN 100 309: Dog 90-Day Oral (Gavage) Repeat Dose Study"; (P.W. Harvey; Schering Agrochemicals Ltd., Chesterford Park Research Station, Saffron, Walden, Essex, CB10 1XL, England; Report No. A81790; 10/10/91); Four beagle dogs/sex/group were dosed orally by gavage with 0, 6, 80 or 1000 mg/kg/day of Technical SN 100 309 (code/batch no. CR 19325/3; purity: 97.9% (2/7/90), 97.7% (5/21/90), 98.0% (7/17/90)) for 13 weeks. The dose for the 1000 mg/kg group was adjusted to 800 mg/kg/day after 6 days of treatment due to excessive vomiting. One male dog in the high dose group died as a consequence of a dosing accident on day 6. It was replaced by another dog which received the same number of doses as the remaining members of the group. Vomiting was the primary clinical sign exhibited by the high dose animals. During the first 6 days, all eight of the animals suffered episodes of emesis (no. of incidences: 25 out of a possible 48 observations). As a consequence, the mean body weight gain and food consumption was less than that of the controls during this time period. The emesis was still evident in a dose-related manner after the dose level was adjusted to 800 mg/kg/day (no. of animals affected/no. of incidences: (M) 0: 2/2, 6: 1/1, 80: 3/4, 800: 4/19, (F) 0: 1/1, 6: 0/0, 80: 4/9, 800: 4/39). The mean water consumption of both sexes in the 80 and 1000/800 mg/kg treatment groups was less than that of the controls during the study. The particular toxicological significance of this observation was not readily apparent. The mean total white blood cell and neutrophil counts for the 1000/800 mg/kg group were greater than those of the control after either 4 or 13 weeks of treatment ($p<0.05$). The mean serum cholesterol and total bilirubin concentrations were less than those of the controls after either 4 and/or 13 weeks of treatment ($p<0.05$ or 0.01). There were no treatment-related effects upon mean absolute or relative organ weights. No lesions were evident in the histopathological examination. **No adverse effect indicated. Subchronic NOEL:** 6 mg/kg/day (based upon the increased incidence of emesis in the 80 mg/kg/day treatment group). **Study acceptable.** (Moore, 1/14/05)

Mouse 28-Day Dietary Toxicity Study

52950-0113, -0114; 205739, 205740; "Technical SN 100 309: Mouse 28-Day Dietary Repeat Dose Study"; (P.W. Harvey; Schering Agrochemicals Limited, Chesterford Park Research Station, Saffron Walden, Essex CB10 1XL, Great Britain; Report No. TOX/89/223-12; 7/19/91); Five CD-1 mice/sex/group received 0, 1000, 3000, 10000 or 30000 ppm of Technical SN 100 309 (code/batch no. CR 19325/2, purity: 95.6%) in the diet for 28 days ((M) 0, 167, 567, 1960 mg/kg/day, (F) 0, 236, 667, 2357 mg/kg/day). All of the animals in the 30000 ppm group died within the 1st week of the study. During that first week, one or more animals in the 30000 ppm group demonstrated signs of reduced activity, ataxia, prostration, tremors, dyspnea, hypothermia, general pallor, ptosis and emaciation. One or more females in the 10000 ppm group exhibited signs of emaciation, general pallor and/or piloerection. The mean body weights of both sexes in the 10000 ppm group were lower than those of the controls throughout the study (NS). Food consumption was reduced in a dose-related manner for the females during the 1st two weeks of the study. The hematology parameters were not affected in a dose-related manner. In the clinical chemistry evaluation, the mean serum cholesterol level of the 10000 ppm females was greater than that of the control ($p<0.01$). The mean relative liver weight of the females in this group as well was greater than that of the control ($p<0.01$). In the histopathology examination, pigmentation of the follicular cells in the thyroid was noted for both sexes in the 10000 ppm group. **Possible adverse effect:** ataxia and tremors. **Subacute NOEL:** (M/F) 3000 ppm ((M) 567 mg/kg/day, (F) 667 mg/kg/day) (based upon the incidence of follicular cell pigmentation in the thyroid and lower mean body weight of the 10000 ppm treatment group); **Study supplemental.** (Moore, 11/23/04)

Mouse Subchronic Dietary Toxicity Study

52950-0136, -0137; 205772, 205773; "Technical SN 100 309 (CR 19325/3): Mouse 90-Day Dietary Repeat Dose Study"; (P.W. Harvey, S.J. Rees; Schering Agrochemicals Ltd., Chesterford Park Research Station, Saffron, Walden, Essex, CB10 1XL, England; Report No. A81792; 11/4/91); Twenty CD-1 mice/sex/group received 0, 80, 900 or 10000 ppm of Technical SN 100 309 (code/batch no. CR 19325/3; purity: 97.9% (2/7/90), 97.9% (5/7/90), 97.7% (7/17/90)) in the diet for 90 days ((M) 0, 12, 139, 1864 mg/kg/day, (F) 0, 18, 203, 2545 mg/kg/day). One 10000 ppm female was found dead on day 43. Death resulted from an accident. The mean body weight

gain of both sexes in the 10000 ppm group was lower than that of the controls over the course of the study. There was no apparent treatment-related effect on food or water consumption. No treatment-related effect was evident in the hematology examination. Although some of the clinical chemistry parameters demonstrated a statistical significance when the values for treated groups were compared to those of the control, there was no apparent dose-related response. The mean relative liver weights for both sexes in the 10000 ppm group were greater than those of the controls ($p<0.01$). However, no treatment-related lesions were noted in the livers of these animals in the histopathologic examination. Exfoliative necrosis of the follicular cells was noted In the thyroid of the 10000 ppm males (0: 0/10 vs. 10000: 8/10). Pigmentation of the follicular cells was noted for both sexes in the 10000 ppm group ((M) 0: 0/10 vs. 10000: 10/10, (F) 0: 0/10 vs. 10000: 9/10). In addition, the 10000 ppm females exhibited urothelial hyperplasia in the urinary bladder (0: 0/10 vs. 10000: 3/10) and uroliths in the lumen of the bladder ((0: 0/10 vs. 10000: 3/10). **Possible adverse effect:** toxic effect on the thyroid gland. **Subchronic NOEL:** (M/F) 900 ppm ((M) 139 mg/kday/day; (F) 203 mg/kg/day) (based upon thyroid effects noted for the 10000 ppm treatment group). **Study supplemental.** (Moore, 1/12/05)